EXHIBIT B

DR. SAMUEL HAMMAR – JANUARY 2007 REPORT

General Health Effects of Non-occupational/Environmental Exposure to Asbestos

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January 16, 2007

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INTRODUCTION

My name is Samuel P. Hammar, M.D. I am board certified in anatomic and clinical pathology. I am the Director of Diagnostic Specialties Laboratory in Bremerton, Washington and am a Clinical Professor of Pathology and Environmental Sciences at the University of Washington Medical Center. I am a member of the U.S.-Canadian Mesothelioma Panel and a member of the International Mesothelioma Panel.

I am the co-editor of *Pulmonary Pathology*, a 1,650 page textbook on the pathology of the lungs and chest cavity, and of *Pulmonary Pathology Tumors* which discusses the various neoplasms of the lung and chest cavity. I am co-author of Chapter 28 in *Pulmonary Pathology* titled *Asbestos* (the other co-author was Dr. Ronald F. Dodson, currently of ERI Analytical in Tyler, Texas, with whom I do research). I am the author of Chapter 32 in *Pulmonary Pathology* dealing with common lung neoplasms, and of Chapter 34 which deals with pleural diseases, 90% of which discusses the entity mesothelioma. The 3rd edition of Dail-Hammar *Pulmonary Pathology* is scheduled to be published in 2007. I am co-editor of the book titled *Asbestos: Risk Assessment, Epidemiology and Health Effects* published in 2006. The other co-editor was Dr. Ronald F. Dodson. I am co-author of a book published by the International Mesothelioma Panel titled *Pathology of Malignant Mesothelioma.* I have written numerous chapters in other books concerning mesothelioma and asbestos-induced diseases and have published approximately 40 articles in peer-reviewed journals on asbestos-related lung diseases.

I was the Chairman of the Pathology Section of the Lung Cancer Study Group that was in existence from 1977 to 1989. The main objective of the study group was to determine new and better ways to treat lung cancer and mesothelioma. My job was to make certain the diagnosis of each individual case was correct and that the tumor in each individual case was properly anatomically staged. I was the pathologist for the CARET study (carotene and retinoic acid efficacy trial) concerning whether anti-oxidant vitamins prevented or reduced the incidence of lung cancer and/or mesothelioma in individuals who were exposed to asbestos and/or cigarette smoke. I was a member of the WHO Committee that wrote a book published in 1999 on the current classification of lung cancer and mesothelioma. I was a contributor to a book recently published by the IARC Press titled *Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart.*

As a pathologist in Bremerton, Washington, I evaluate asbestos-induced lung disease on a regular basis since Bremerton is the home of the Puget Sound Naval Shipyard and is a small city in which a significant percentage of the population has been exposed to asbestos. As a pathologist, I see approximately 10-20 new mesothelioma cases per year in Bremerton, 20-30 cases of asbestos-induced lung disease (pleural and/or parenchymal) per year, and approximately 20 cases of primary lung cancer per year related to asbestos.

I was asked by Lane Andrae, Paralegal, of the Motley Rice Law Firm, Mount Pleasant, South Carolina, to provide general information concerning the health effects of non-occupational and environmental exposure to asbestos.

A copy of my curriculum vitae is attached to my expert report, as is a copy of the trials and depositions in which I have participated between 2002 and 2006. My hourly consultation rate is $500.00 per hour.

ASBESTOS

It is well recognized that asbestos causes cancer and non-cancerous diseases. The primary cancers caused by asbestos exposure are mesothelioma and lung cancer. Asbestos, in high concentrations, can cause cancer of the upper aerodigestive system, GI tract and kidney. Non-neoplastic diseases caused by asbestos include benign asbestos-induced pleural effusion, diffuse visceral pleural fibrosis, localized visceral pleural fibrosis with invagination into lung parenchyma (round atelectasis), diffuse pleural fibrosis, localized pleural fibrosis (hyaline pleural plaque), and asbestosis.

As discussed in the Helsinki Consensus Report, all forms of asbestos are capable of causing all neoplastic and non-neoplastic diseases. All asbestos-related diseases are dose-response related, which means the more asbestos an individual is exposed to, the greater the risk of developing one of those diseases. The Helsinki Consensus Report indicates one can attribute causation of mesothelioma to asbestos if there is a reliable history of exposure to asbestos, even if it is a low exposure (Anonymous. Asbestos, asbestosis and cancer: The Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health 1997;23:311-316).

As extensively discussed in the Third Wave Book concerning asbestos in place (The Third Wave of Asbestos Disease: Exposure to Asbestos in Place. Annals of NY Acad of Science 1991;643:416-444 and 509-624), it is well documented that low levels of asbestos are potentially capable of causing these diseases, especially mesothelioma. Mesothelioma has been found to be caused by asbestos in extremely low concentrations: (A) Hodgson JT, Darnton A. The Quantitative Risks of Mesothelioma and Lung Cancer in Relation to Asbestos Exposure. Ann Occup Hyg 2000;44:565-601; (B) Iwatsubo Y, Pairon JC, Boutin C, Menard O, et al. Pleural Mesothelioma: Dose-Response Relation at Low Levels of Asbestos Exposure in a French Population-based Case-Control Study. Am J Epidemiol 1998;148:133-42; (C) Rolland P, et al. Risk of Pleural Mesothelioma: A French population-based case-control study (1998-2002). Lung Cancer 2006;54:S9-S10.

The Federal Register in 1986 (Federal Register 1986;51:22644) also provided information on low level exposure to asbestos and the development of mesothelioma by stating only 0.1 f/cc years would cause an excess of 6.9 mesotheliomas per 1,000 individuals exposed. This would be about 70 times what is considered to be the background level.

Experimental studies in rats by direct intraperitoneal injection showed that UICC chrysotile asbestos is just as potent as amosite or crocidolite asbestos (Rittinghausen S., et al. Atypical malignant mesotheliomas with osseous and cartilaginous differentiation after intraperitoneal injection of various types of mineral fibers in rats. Exp Toxicol Pathol 1992;44:55-58). The issue sometimes arises that chrysotile has to be contaminated with tremolite to be tumorigenic with respect to mesothelioma development. Whether this is true or not is still under investigation, although as pointed out by Egilman et al., all chrysotile from Canada is contaminated with tremolite (Egilman D., et al. Exposing the "myth" of ABC, "Anything but Chrysotile" Am J Ind Med 2003;44:540-557).

With respect to how much asbestos it takes to cause mesothelioma is still open to discussion. In 1999 Hillerdal published an article concerning mesothelioma in non-occupational and low-dose exposure (Hillerdal G. Mesothelioma: cases associated with non-occupational and low dose exposures. Occup Environ Med 1999;56:506-513). One article cited by Hillerdal was that by Vianna and Polan (Vianna NJ and Polan AK. Non-occupational exposure to asbestos and malignant mesothelioma in females. Lancet 1978;1:1061-1063). In that article, cases of mesothelioma were described in women who had bystander exposure to asbestos from their husband or father. These were considered to be low level exposures to chrysotile asbestos and gives further support to the notion that even low levels of chrysotile asbestos cause mesothelioma. Other articles have also shown the development of mesothelioma caused by chrysotile from relatively short and low concentrations (Scansetti et al., Pleural mesothelioma after a short interval from first exposure in the wine filter industry. Am J Ind Med 1984;5:335-339). In addition, cases of mesothelioma were reported in pet dogs whose owners had asbestos-related occupations or asbestos-related hobbies (Glickman LT et al. Mesothelioma in pet dogs associated with exposure of their owners to asbestos. Environ Res 1983;32:305-313). Mesotheliomas also occurred in dogs who were treated with flea repellants that contained asbestos. In the dogs' lung tissue that was examined, chrysotile was usually the dominant type of asbestos fiber found.

The primary site of most mesotheliomas is in the pleura. With respect to what fibers are found in the pleura, Suzuki et al. published that chrysotile is the predominant fiber found in the pleura and most of the chrysotile fibers are less than 2 μm long. (A) Suzuki Y, Yuen SR. Asbestos tissue burden study on human malignant mesothelioma. Ind Health 2001;39:150-160; (B) Suzuki Y, Yuen SR. Asbestos fibers contributing to the induction of human malignant mesothelioma. Ann N Y Acad Sci 2002;982:160-176; (C) Suzuki Y et al. Short, thin asbestos fibers contribute to the development of human malignant mesothelioma: pathological evidence. Int J Hyg Environ Health 2005;208:201-210; and (D) Suzuki Y, Kohyama N. Translocation of inhaled asbestos fibers from the lung to other tissues. Am J Ind Med 1991;19:701-704.

The World Health Organization has recently (2006) proposed that there is no safe level of exposure to asbestos. The WHO in 1998 published a document on chrysotile asbestos stating there was no threshold below which chrysotile asbestos could not act as a carcinogenic factor in causing the development of lung cancer or mesothelioma (WHO Policy paper [draft] "Elimination of Asbestos-related diseases;" and WHO document on chrysotile asbestos – Environmental Health Criteria 203, 1998).

A recent article by Pan et al. suggested that true environmental exposure to asbestos in California may result in the development of mesothelioma (Pan XL et al. Residential proximity to naturally occurring asbestos and mesothelioma risk in California. Am J Respir Crit Care Med 2005;172:1019-1025). The predominant form of asbestos found in central California is chrysotile asbestos.

Various governmental agencies have written laws to protect people from asbestos in place. Primarily, this is done so that when a dwelling of some type contains asbestos and is going to be altered, either by remodeling or demolishment, the individuals who perform the remodeling/demolishing are not exposed to asbestos, nor are the residents residing in the building and the environment surrounding these dwellings are exposed to asbestos.

With respect to sampling of air for the presence of asbestos fibers, the most frequent analysis that has been used in the past is phase-contrast microscopy. This methodology typically identifies fibers 5 μm long and fibers less than .25 μm in diameter. A significant number of asbestos fibers are not counted using this technology. Therefore, there can be significant underestimation of the asbestos concentration in air that an individual may be exposed to as a result of demolishing/remodeling buildings. Transmission electron microscopy is currently the method of choice for accurately identifying concentrations of asbestos in air (Dodson RF, Hammar SP (Eds). Asbestos: Risk Assessment, Epidemiology and Health Effects. Boca Rator: CRC Press/ Taylor Francis Group; 2006:9-39).

Sam Hammar

ASBESTOS-INDUCED LUNG AND PLEURAL DISEASE

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September 13, 2006

INTRODUCTION

My name is Samuel P. Hammar, M.D. I am board certified in anatomic and clinical pathology. I am the Director of Diagnostic Specialties Laboratory in Bremerton, Washington and am a Clinical Professor of Pathology and Environmental Sciences at the University of Washington Medical Center. I am a member of the U.S.-Canadian Mesothelioma Panel and a member of the International Mesothelioma Panel.

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As a pathologist in Bremerton, Washington, I evaluate asbestos-induced lung disease on a regular basis since Bremerton is the home of the Puget Sound Naval Shipyard and is a small city in which a significant percentage of the population has been exposed to asbestos. As a pathologist, I see approximately 10-20 new mesothelioma cases per year in Bremerton, 20-30 cases of asbestos-induced lung disease (pleural and/or parenchymal) per year, and approximately 20 cases of primary lung cancer per year related to asbestos.

I was asked by Mr. Nathan Finch of Caplin & Drysdale, counsel to W.R. Grace Asbestos Personal Injury Claimants Committee, to provide general information concerning asbestos and information on asbestos-induced diseases for the W.R. Grace hearing.

A copy of my curriculum vitae is attached to my expert report, as is a copy of the trials and depositions in which I have participated between 2002 and 2006. My hourly consultation rate is $500.00 per hour.

INFORMATION ABOUT ASBESTOS

Asbestos is a naturally occurring fibrous mineral with unique properties that has resulted in it being used in numerous products. Asbestos is a lightweight, thermally and/or chemically resistant material with high tensile strength that, because of these qualities, has been extensively used in over 3,000 products. Asbestos has extensively been used as a fire retardant and insulating material. A relatively brief history of asbestos was published by Abratt et al. (Abratt RP, Vorobiof DA, White N. *Asbestos and mesothelioma in South Africa.* Lung Cancer 2004;45S:S3-S6). As early as 4000 BCE (before Christian era), asbestos was used for wicks in lamps and candles. "Asbestos" means inextinguishable or unquenchable. From 2000-3000 BCE, embalmed bodies of Egyptian pharaohs were wrapped in asbestos clothes to offset the ravages of time. In 2500 BCE, asbestos was used in Finland to strengthen clay pots. From 800-900 AD, there was anecdotal evidence that Charlemagne's tablecloth was made from woven asbestos. During 1000 AD, Mediterranean people used chrysotile from Cyprus and tremolite from upper Italy for the fabrication of cremation clothes, mats and wicks for temple lamps. During the period 1300-1400, Marco Polo visited an asbestos mine in China in the latter half of the 13th century and concluded that asbestos was a stone. He laid to rest the myth that asbestos was the hair of a woolly lizard. During the early 1700s, asbestos papers and boards were made in Italy. In 1724 Benjamin Franklin brought a purse made of asbestos to England. The purse is now in the Natural History Museum. In 1828 a U.S. patent was issued for asbestos insulating material to be used in steam engines. In 1853 asbestos helmets and jackets were worn by the Parisian Fire Brigade. In 1866 molded lagging material was made from water, glass and asbestos. In 1896 the first asbestos brake linings were made by Ferodo Ltd., in England. In 1900 high pressure asbestos gaskets were made by Klinger in Austria. In 1913 asbestos pipes were first developed in Italy. In 1919 standard corrugated sheet asbestos was introduced in Australia by Hardies. From 1939 to 1945, wartime use included fireproof suits and parachute flares. In 1939 in the film "The Wizard of Oz," the Wicked Witch of the West appeared on a broom made of asbestos. From 1945 to 1975, post-war construction projects relied heavily on the use of asbestos, reaching an all-time high in 1973. During the 1990s, the solid fuel boosters of the space shuttle were insulated with asbestos, one of the few remaining current uses. Brake linings continue to contain asbestos, usually chrysotile asbestos, and pose a health risk to workers and their families (Lemen RA. *Asbestos in brakes: exposure and risk of disease.* Am J Ind Med 2004;45:229-237; and Egilman DS, Billings MA. *Abuse of epidemiology: Automobile manufacturers manufacture a defense to asbestos liability.* Int J Occup Environ Health 2005;11:360-371).

Gee and Greenberg published an excellent review of asbestos and its adverse effects on health and the delay in recognizing the adverse effects on health (Gee D, Greenberg M. *Asbestos: from 'magic' to malevolent mineral.* In: Late lessons from early warnings: the precautionary principle 1896-2000). A summary of the lessons of the asbestos story is provided in their chapter on pages 59 through 61 (see section 5.7 in their chapter). Included in their chapter is France's ban on all types of asbestos (Table 5.1 from their chapter).

Widespread use of asbestos-containing materials resulted in exposures of millions of individuals who were then at risk for developing asbestos-related diseases. Asbestos-related diseases typically have a long latency period (time from first exposure to diagnosis of disease). Asbestos has been shown to produce two basic disease processes: cancer and scarring.

Cancer diseases caused by asbestos include lung cancer, mesothelioma and other cancers such as cancers of the digestive tract and kidney. The scarring diseases include the disease *asbestosis* (scarring of the supportive framework of the lung), *visceral pleural fibrosis*, *hyaline*

pleural plaque, *round atelectasis* and *fibrothorax*. Asbestos can also cause a pleural effusion many years after a person was last exposed to asbestos and can cause unusual and localized diseases in the lung.

Asbestos is sometimes stated to be ubiquitous in our environment and that all individuals are exposed to asbestos every day. This is incorrect. The majority of individuals under age 30 have not been exposed to asbestos and will not be exposed to asbestos except under rare circumstances. At this time, the majority of air samples analyzed from the general environment do not contain asbestos. In cities where air fiber analysis has been done, levels of asbestos have been in the range of 0.0005-0.00005 fibers per cubic centimeter. Numbers of asbestos fibers in buildings vary depending on the age of the building, what materials were used to insulate the building and how much disrepair the building was in (In: Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of asbestos-associated disease.* Boston: Little Brown & Company 1992;29-30). In 1999 Dodson et al. evaluated tissue burden of asbestos in nonoccupationally exposed individuals from East Texas, a geographical location in which there was considerable use of asbestos. Three-fourths of the 33 individuals in East Texas had no asbestos bodies in their lung tissue and 1/3rd of the 33 individuals had no asbestos fibers in their lung tissue. This was age dependent, with younger individuals characteristically having no asbestos and older individuals having either a small amount of chrysotile asbestos or occasionally having amphibole asbestos (Dodson RF, Williams MG, Huang J, Bruce JR. *Tissue burden of asbestos in nonoccupationally exposed individuals from East Texas.* Am J Ind Med 1999;35:281-286).

The body has natural defense mechanisms to try to protect it from dusts like asbestos and other particulate matter. These defense mechanisms include the mucus and hairs in the nose; the epithelial lining of bronchi, which include ciliated cells and mucous secreting cells that are part of the system referred to as the "mucociliary escalator apparatus" that clears particulates from the lining of the air tubes; and the alveolar macrophages that engulf particulate matter up to a size of about 5 μm in greatest dimension. Despite these clearance mechanisms, occupationally exposed individuals can have over 60 million asbestos fibers per gram of dry lung tissue and over 1 million asbestos bodies per gram of dry lung tissue (Dodson RF, O'Sullivan M, Corn CJ, McLarty JW, Hammar SP. *Analysis of asbestos fiber burden in lung tissue from mesothelioma patients.* Ultrastruct Pathol 1997;21:321-336).

Asbestos is cleared from the lung over time, which might explain observations in the 1950s that as individuals became older, the number of asbestos bodies found in their lung tissue decreases. Chrysotile fibers are thought to be more readily cleared from the lung than amphibole fibers. Chrysotile has a half-life in the lung of approximately 90-120 days. (A) Churg A, Green FHY. *Occupational Lung Disease.* In: Thurbeck WM, Churg AM, eds., Pathology of the lung, 2nd Ed. New York: Thieme, 1995:851-929; (B) Roggli VL, Brody AR. *Experimental models of asbestos-related diseases.* In: Roggli VL, Greenberg SD, Pratt PC, eds., Pathology of asbestos-associated diseases. Boston: Little, Brown & Co. 1992:257-297; (C) Churg A. *Nonneoplastic diseases caused by asbestos.* In: Churg A, Green FHY, eds., Pathology of occupational lung disease. New York: Igaku-Shoin, 1988:213.277; (D) Jones DH, Vincent JH, Addison J, et al. *The fate and effect of inhaled chrysotile asbestos fibers.* Ann Occup Hyg 1994;38, suppl 1:619-629. Clearance of short fibers is significantly greater than clearance of longer fibers. Amphiboles are cleared from lung and have a half-life in lung tissue of about 20 years for amosite and approximately 5-10 years for crocidolite. (A) Churg A, Vedal S. *Fiber burden and patterns of asbestos-related disease in workers with heavy mixed amosite and chrysotile exposure.* Am J Respir Crit Care Med 1994;150:663-669; (B) Berry G, Rogers AJ, Pooly RD. *Mesotheliomas – asbestos exposure and lung burden.* IARC 1989;90:486-496; (C) Du Toit RS. *An estimate of the rate at which crocidolite asbestos fibers are cleared from the*

lung. Ann Occup Hyg 1991;35:433-438; (D) de Klerk NH, Musk AW, Williams VM, et al., *Comparison of measures of exposure to asbestos in former crocidolite workers from Wittenoom Gorge, Western Australia.* Am J Ind Med 1996;30:579-587). However, de Klerk could find no difference between the clearance rates of long and short fibers, and Oberdörster estimated human clearance half-lives to be about 90-100 days for chrysotile and 200-1500 days for crocidolite fibers >16 µm in length based on extrapolated rat and primate inhalation data (Oberdörster G. *Macrophage-associated responses to chrysotile.* Ann Occup Hyg 1994;38:601-615).

The concentration of asbestos found in the lung tissue of individuals in the general population without occupational or bystander exposure to asbestos is age-dependent. For example, the upper limits of normal reported by Churg and Warnock were 100 asbestos bodies per gram of wet lung tissue, whereas Roggli, Dodson and Hammar reported 20 asbestos bodies per gram of wet lung tissue as the upper limits of normal in most adults (Hammar SP, Dodson RF. *Asbestos.* Chapter 28. In: Dail DH, Hammar SP, eds., Pulmonary Pathology, 2nd Ed. New York: Springer-Verlag, 1994:901-983). In Western Washington, about 50% of women whose lung tissue has been analyzed by digestion analysis have no asbestos bodies, whereas most men have asbestos bodies (personal observation). In our evaluation of mesothelioma patients' lung tissue, there is considerable variation in the concentration of asbestos found in individuals with the same disease (Dodson RF, O'Sullivan M, Corn CJ, McLarty JW, Hammar SP. *Analysis of asbestos fiber burden in lung tissue from mesothelioma patients.* Ultrastruct Pathol 1997;21:321-336). What is not known at this point in time is how much asbestos it actually takes to produce a given disease. Published data suggests it requires higher concentrations of asbestos to cause lung cancer and asbestosis than it does to cause mesothelioma and pleural plaques (*Asbestos, asbestosis and cancer: the Helsinki criteria for diagnosis and attribution.* Scand J Work Environ Health 1997;23:311-316).

The mechanism by which asbestos causes disease is not totally understood, although a significant amount of information has been recorded. As reviewed by Kamp and Weitzman, asbestos can cause injury by direct interaction with the cells or can cause certain types of chemical reactions to occur such as the development of oxygen and nitrogen free radicals that can cause injury (Kamp DW, Weitzman SA. *The molecular basis of asbestos induced lung injury.* Thorax 1999 Jul;54(7):638-52; and Atkinson MAL. *Molecular and cellular responses to asbestos exposure.* In: Dodson RF, Hammar SP, eds. Asbestos: Risk assessment, epidemiology, and health effects. Boca Raton, CRC, Taylor-Francis, 2006:91-136). Of interest, it appears that for every adverse reaction that asbestos causes in the human body, there is an opposite reaction that tries to repair that injury. Why some individuals develop an asbestos-related disease and others do not when both are exposed to the same amount of asbestos is unknown, although this is thought to be due to individual susceptibility and is probably genetically related, although exact mechanisms are not well understood. There has been published evidence that glutathione S-transferase activity is inversely correlated with the development of lung cancer and asbestosis. (A) Abidi P, Afaq F, Arif JM, et al. *Chrysotile-mediated imbalance in the glutathione redox system in the development of pulmonary injury.* Toxicol Lett. 1999; May 20;106(1):31-9; (B) Kelsey KT, Nelson HH, Wiencke JK, et al. *The glutathione S-transferase theta and mu deletion polymorphisms in asbestosis.* Am J Ind Med 1997 Mar;31(3):274-9; (C) Hirvonen A, Saarikoski ST, Linnainmaa K, et al. *Glutathione S-transferase and N-acetyltransferase genotypes and asbestos-associated pulmonary disorders.* J Natl Cancer Inst 1996 Dec 18;88(24):1853-6; (D) Anttila S, Luostarinen L, Hirvonen A, et al. *Pulmonary expression of glutathione S-transferase M3 in lung cancer patients: association with GSTM1 polymorphism, smoking and asbestos exposure.* Cancer Res 1995 Aug 1;55(15):3305-9; (E) Smith CM, Kelsey KT, Wiencke JK, et al. *Inherited glutathione-S-transferase deficiency is*

a risk factor for pulmonary asbestosis. Cancer Epidemiol Biomarkers Prev 1994 Sep;3(6):471-7.

Studies are now underway to determine if serum markers for osteopontin (Cullen MR. *Serum osteopontin levels—is it time to screen asbestos-exposed workers for pleural mesothelioma?* N Engl J Med 2005;353:1564-73) and soluble mesothelin-related peptides are useful in the early detection of mesothelioma (Robinson BW, Creaney J, Lake R, et al. *Mesothelin-family proteins and diagnosis of mesothelioma.* Lancet 2003;362:1612-6).

All asbestos-related diseases are dose-response related and it has generally been observed that the longer one has been exposed to asbestos and the greater the concentration of asbestos is in an individual's body, the greater risk that individual has for developing an asbestos-related disease. What can't be determined at the present time is which person who has been exposed to asbestos will eventually develop an asbestos-related disease. In any given disease, there is always a range of concentration of asbestos that one finds in the lung or pleural tissue of such individuals.

Because one cannot tell which exposures caused a mesothelioma or lung cancer, one cannot state that one exposure to asbestos caused the disease and another exposure did not. All exposures to all types of asbestos fibers act in concert to produce disease; it is the cumulative exposure to asbestos fibers that cause the disease.

MESOTHELIOMA

Mesotheliomas are malignant tumors that arise from the lining of the body cavities. During embryogenesis, a single body cavity called the celomic cavity is divided into the pleural (chest), peritoneal (abdominal) and pericardial (heart) cavities (Hammar SP. *Pleural diseases.* Chapter 34. In: Dail DH, Hammar SP. eds., 2nd Ed. Pulmonary Pathology. New York: Springer-Verlag, 1994:1463-1579; and Galateau-Salle F. Pathology of malignant mesothelioma. Springer-Verlag, 2006). These cavities are lined by a thin, almost invisible membrane similar in appearance to thin plastic wrap made up of an outer mesothelial layer and underlying connective tissue component, the entire thickness being approximately 0.4 mm. Mesotheliomas are neoplasms derived from the cells that form this membrane. Mesotheliomas begin as small nodules that originate from cells that form these membranes and, over time, coalesce to form a rind that encases the organ(s) within the respective body cavity. Approximately 90-95% of mesotheliomas develop in the chest cavity and are called *pleural mesothelioma*. Five to 10% develop in the abdominal cavity and are called *peritoneal mesothelioma*. Rare mesotheliomas arise from the pericardium and from tunica vaginalis, the latter being an invagination of the peritoneum. Benign mesothelial nodules called *adenomatoid tumors* occur in epididymis, uterus and rarely the pleura. Adenomatoid tumors can be mistaken for malignant mesothelioma.

Mesotheliomas are divided into four histologic tissue types based on what the cancer cells look like when viewed through a light microscope: 1) epithelial mesothelioma; 2) sarcomatoid (fibrous) mesothelioma; 3) biphasic mesothelioma; and 4) desmoplastic mesothelioma. Mesotheliomas show a marked variability in how they look microscopically that can cause difficulty in accurately diagnosing them.

The only epidemiologically established cause of mesothelioma is asbestos. Approximately 90% of mesotheliomas in men are caused by asbestos and in our experience, 70% of mesotheliomas in women are caused by asbestos (Hammar SP, Roggli VL, Oury TD. *Malignant mesothelioma in women.* Lung Cancer 1977;18, suppl 1:236). Most women who develop mesothelioma thought to be caused by asbestos had domestic bystander exposure to asbestos. Dodson et al., (Dodson RF, O'Sullivan M, Brooks DK. Hammar SP. *Quantitative analysis of asbestos burden in women with mesothelioma.* Am J Ind Med 2003;43:188-195) reported 16 cases of mesothelioma in women whose lung tissue was evaluated for asbestos fiber concentration by digestion analysis. Several women with domestic bystander exposure to asbestos had slightly elevated concentrations of asbestos in their lung tissue. In addition, Dawson et al., (Dawson A, Gibbs AR, Pooley FD, Griffiths SM, Hoy J. *Malignant mesothelioma in women.* Thorax 1993;48:269-274) reported that approximately 80% of mesothelioma in women were related to asbestos. In four women who stated they were not exposed to asbestos, over 2 million asbestos fibers per gram of dry lung tissue were identified by asbestos digestion analysis, thus suggesting that individuals may not know how they were exposed to asbestos.

Leigh et al. (Leigh J, Davidson P, Hendrie L, Berry D. *Malignant mesothelioma in Australia, 1945-2000.* Am J Ind Med 2002;41:188-201) stated that when earlier cases of mesothelioma that were classified as "no history of exposure" were reviewed, it was found that 57 of the 203 so classified cases had a history of asbestos exposure recorded. Thus, only 19% had no known history. Leigh and colleagues stated that of the "no known history" group, 81% had fiber counts greater than 200,000 fibers/gram dry lung and 30% had more than 10^6 fibers per gram of dry lung greater than 2 μm long, including some fibers longer than 10 μm. The authors pointed out that dust exposure is not always recognized as such and it was more likely to be seen in cases of women than men. It was also pointed out that even in the absence of asbestos fibers

in the lung, it did not negate the possibility that asbestos fibers could have initiated mesothelioma and then be cleared to another site.

Other causes of mesothelioma have been reported, although are rare. Most non-asbestos causes of mesothelioma were reported by Peterson et al. (Peterson JT Jr, Greenberg SD, Buffler PA. *Non-asbestos-related malignant mesothelioma: a review.* Cancer 1984;54:951-960). Potentially, malignant mesothelioma can develop at the site of serosal injury caused by any agent. Most causes cited by Peterson et al. have not withstood the test of time. At this point in time, therapeutic radiation given to treat other tumors is thought to be causative of mesothelioma, as are some cases of chronic injury to the serosal lining of body cavities. One recent issue that has arisen concerning mesothelioma causation concerns SV40 virus. As most recently reported in Nature Reviews, Cancer in December 2002, there is no proof at this time that SV40 virus causes mesothelioma, although investigation is ongoing (Gazdar AF, Butel JS, Carbone M. *SV40 and human tumours: myth, association or causality?* Nat Rev Cancer 2002 Dec;2:957-64). The most recent articles on the potential for SV40 virus to cause mesothelioma have suggested there is no association between SV40 virus and the development of mesothelioma (Manfredi JJ, Dong J, Liu W, et al. *Evidence against a role for SV40 in human mesothelioma.* Cancer Res 2005;65:2602-2609; and Lopez-Rios F, Illei PB, Rusch V, Ladanyi M. *Evidence against a role for SV40 infection in human mesotheliomas and high risk of false-positive PCR results owing to presence of SV40 sequences in common laboratory plasmids.* Lancet 2004;364:115-1166). Erionite, a fibrous zeolite, has been reported to cause mesothelioma in individuals in Central Turkey who use erionite in various construction activities. A recent report stated all cases of mesothelioma caused by erionite occurred only in individuals who were related to each other (Emri S, Demir AU. *Malignant pleural mesothelioma in Turkey, 2000-2002.* Lung Cancer 2004 Aug;45 Suppl 1:S17-20; and Dogan AU, Baris YI, Dogan M, Emri S, Steele I, Elmishad AG, Carbone M. *Genetic predisposition to fiber carcinogenesis causes a mesothelioma epidemic in Turkey.* Cancer Res 2006;66:5063-5068).

The World Health Organization's recently drafted policy paper titled "Elimination of Asbestos-related Diseases" pointed out that all types of asbestos are capable of causing asbestosis, lung cancer, mesothelioma and other cancers. The general consensus at this point in time is there is no minimal threshold dose of inhaled asbestos below which there is no increased risk of mesothelioma. A 2000 review article on the quantitative risks of mesothelioma related to asbestos exposure by Hodgson and Darnton adopted a "no threshold" approach. As set forth in Table 11 in their review on dose-response relationships between asbestos and mesothelioma, Hodgson and Darnton estimated that a cumulative exposure of 1 fiber/mL-year for crocidolite yields a lifetime risk "best" estimate of about 650 mesothelioma deaths/100,000 (range = 250-1500), 90/100,000 for amosite (range = 15-300), and 5/100,000 for chrysotile (range = 1-20). For a cumulative exposure of 0.1 fibers/mL-years, these authors set forth a "best" estimate of about 100 deaths per 100,000 exposed for crocidolite with a highest arguable estimate of 350 and a lowest of 25; for amosite, the corresponding figures were 15 deaths per 100,000 with a highest arguable estimate of 80 and a lowest of 2; at this level of exposure, the risk for chrysotile was "probably insignificant," with a highest arguable estimate of 4 deaths per 100,000. For a cumulative exposure of 0.01 fibers/mL-years, the "best" estimate was about 20 deaths per 100,000 exposed for crocidolite with a highest arguable estimate of 100 and a lowest of 2; for amosite, the corresponding figures were 3 deaths per 100,000 with a highest arguable estimate of 20 and a lowest that was "insignificant;" at this level of exposure, the risk for chrysotile was "probably insignificant" with a highest arguable estimate of 1 death per 100,000.

A review and meta-analysis of the risk of pleural mesothelioma from environmental exposure to asbestos by Bourdes et al. was published in 2000 (Bourdes V, Boffetta P, Pisani P.

Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. Eur J Epidemiol 2000;16:411-7). These authors identified eight relevant studies on the risk of pleural mesothelioma from household or neighborhood exposures. These authors found the relative risk of pleural mesothelioma from household exposure ranged between 4.0 and 23.7 with a summary risk estimate of 8.1 (95% confidence interval: 5.3-12); and for neighborhood exposures the relative risk ranged between 5.1 and 9.3 with a summary estimate of 7.0 (95% confidence interval: 4.7-11). Bourdes et al., stated their review suggested a substantial increase in risk of pleural mesothelioma following high environmental exposure to asbestos, but the data was insufficient to estimate the magnitude of risk at the level of environmental exposure commonly experienced by the general population in industrial countries.

Pan et al. concluded their data supported the hypothesis that residential proximity to naturally-occurring asbestos was significantly associated with increased risk of malignant mesothelioma in California (Pan XL, Day HW, Wang W, Beckett LA, Schenker MB. *Residential proximity to naturally occurring asbestos and mesothelioma risk in California.* Am J Respir Crit Care Med 2005;172:1019-25.

The 1998 WHO/IPCS monograph on chrysotile titled *Environmental Health Criteria 2003: Chrysotile Asbestos* stated in the summary section on page 144 that chrysotile asbestos posed an increased risk for the development of lung cancer and mesothelioma and that no threshold of exposure had been delineated for the carcinogenic risk.

The British Thoracic Society also came to a similar conclusion (British Thoracic Society Standards of Care Committee. Statement on malignant mesothelioma in the United Kingdom. Thorax 2001;56:250-265).

The study of pleural mesotheliomas based on the Swedish Family Cancer Database stated there was an increasing age-adjusted incidence of mesothelioma over the period 1961-1998, not only for occupations expected to be associated with asbestos exposure, but also in professional groups and even farmers (Hemminki K, Li X. *Time trends and occupational risk factors for pleural mesothelioma in Sweden.* J Occup Environ Med 2003;45:456-61).

The review article by Hillerdal in 1999 concerning nonoccupational exposure to asbestos concluded mesothelioma developed as a consequence of low levels of exposure to asbestos (Hillerdal G. *Mesothelioma: cases associated with non-occupational and low dose exposures.* Occup Environ Med 1999;56:505-13).

Iwatsubo et al. found the odds ratio for mesothelioma occurred at very low doses and their data suggested a no threshold model (Iwatsubo Y, Pairon JC, Boutin C, et al. *Pleural mesothelioma: dose-response relation at low levels of asbestos exposure in a French population-based case-control study.* Am J Epidemiol 1998;148:133-42).

A case-referent study reported by Rödelsperger et al. stated the authors found an odds ratio for mesothelioma greater than 4.5 with lung tissue asbestos fiber concentrations in the range of 100,000-200,000 fibers longer than 5 µm per gram of dry lung tissue, and an odds ratio for mesothelioma of about 2 or more recorded for lower lung tissue asbestos fiber concentrations in the range of 50,000-100,000 fibers longer than 5 µm per gram of dry lung tissue (Rödelsperger K, Woitowitz HJ, Bruckel B, et al. *Dose-response relationship between amphibole fiber lung burden and mesothelioma.* Cancer Detection Prevention 1999;23:183-93). In addition, Rödelsperger et al. found an odds ratio of 7.9 with low exposures in the range of anything more

than zero to 0.15 fibers/cc years (Rödelsperger K, Jöckel K-H, Pohlabein H, et al. *Asbestos and man-made vitreous fibres as risk factors for diffuse malignant mesothelioma: results from a German hospital-based case-control study.* Am J Ind Med 2001;39:262-75).

Magnani et al. in a tri-nation case-referent analysis found a moderate to high probability of non-occupational exposure to asbestos in the development of mesothelioma (Magnani C, Agudo A, Gonzalez CA, et al. *Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos.* Br J Cancer 2000;83:104-11).

Hodgson and Darnton estimated the relative potencies for crocidolite, amosite and chrysotile for mesothelioma induction was roughly 500:100:1 respectively (Hodgson JT, Darnton A. *The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure.* Ann Occup Hyg 2000;44:565-601). However, the report by Leigh and Robinson concluded, based on lung tissue amphibole fiber concentrations allowing for clearance half-lives, that the potency ratio for crocidolite, amosite and chrysotile was 26:14:1 respectively (Leigh J, Robinson BWS. *The history of mesothelioma in Australia, 1945-2001.* In: Robinson BWS, Chahinian AP, eds. Mesothelioma. London: Martin Dunitz; 2002:55-86).

Another widely-cited set of potency ratios reported in the literature was 30:15:1 for crocidolite, amosite and chrysotile, respectively (World Trade Organization Dispute Settlement Report WT/DS135. *European Communities – Measures concerning asbestos and asbestos-containing products.* Geneva: WTO;2000. See also WTO Dispute Settlement Reports 2001: Volume VIII: Pages 3303-4047 [DSR 2001:VIII]. Cambridge: Cambridge University Press; 2004).

With respect to mesothelioma causation by asbestos, it is generally accepted that amphibole asbestos is more tumorigenic in causing mesothelioma than chrysotile asbestos on a fiber-for-fiber basis (Hammar SP. *Pleural diseases.* Chapter 34. In: Dail DH, Hammar SP, eds., 2nd Ed. Pulmonary Pathology. New York: Springer-Verlag, 1994:1463-1579). The reported ratio of the variability in tumorigenicity is great. As stated previously, Hodgson & Darnton suggested the tumorigenicity of asbestos fibers on a fiber-for-fiber basis was 500-100-1 for crocidolite-amosite-chrysotile, respectively (Hodgson JT, Darnton A. *The quantitative risk of mesothelioma and lung cancer in relation to asbestos exposure.* Ann Occup Hyg 2000 Dec;44(8):565-601). In contrast, Dr. William Nicholson concluded crocidolite was about 10-12 times more potent than chrysotile in causing mesothelioma and that chrysotile and amosite were approximately equal (Nicholson WJ. *Comparative dose-response relationship of asbestos fiber types: magnitude and uncertainties.* Ann NY Acad Sci 1991 Dec;643:74-84).

Smith and Wright observed that the ten cohorts with the largest number of mesothelioma cases occurred in those in which the dominant exposure to asbestos was chrysotile (Smith AH, Wright CC. *Chrysotile asbestos is the main cause of pleural mesothelioma.* Am J Ind Med 1996 Sept;30(3):252-266). The article by Drs. Smith and Wright argues that the relative dose of asbestos plays just as important a role in causing mesothelioma as the relative potency of a given fiber type.

A relatively recent experimental study looking at the development of mesotheliomas in rats after direct intraperitoneal injection with asbestos and other substances found there was an approximate equal number of mesotheliomas in the rats directly injected with amosite, crocidolite and UICC-chrysotile B, which is a mixture of chrysotile from nine different Quebec chrysotile mines. The vehicle used to inject the asbestos and a non-asbestos substance called wollastonite did not cause mesothelioma (Rittinghausen S, Ernst H, Muhle H, Mohr U. *Atypical*